The Newer Drugs for Allergic Disorders and Their Place in the Histamin Theory*

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ALTHOUGH it has long been known that allergic phenomena are initiated by the union of antigens and their specific antibodies, the intermediary steps between this union and the manifestations of clinical and experimental allergy have been obscure. Such theories as (a) "disturbed colloidal equilibrium of the cell membranes and blood with serum flocculation," (b) "disturbance of the sympathetic-parasympathetic balance of the autonomic nervous system," (c) the "antigen-antibody combination acting as a specific toxin," and (d) the "enzymic action of the combination on body proteins producing toxins," have each had more evidence against it than for it.

In recent years the "Histamine Theory" has come to the fore as the one with the most clinical and experimental evidence for it and the least against. To sum it up, the antigen-antibody union taking place on the cell surfaces causes cell damage and dissolution of cell proteins, with the liberation of an H-substance, presumably histamine, which causes the increased capillary permeability, stimulation of secretions and smooth-muscle spasm characteristic of allergic reactions. The histamine is produced through the abnormal decarboxylization of the amino-acid histidine resulting from the protein decomposition (Figure 1). Ordinarily the shock-organ, skin, nasal mucous membrane, bronchiolar mucosa and smooth muscle, etc., determines which clinical entity is produced, such as urticaria, hay fever, asthma, etc. respectively, but if overwhelming amounts of histamine are released in the circulation the allergic reactions may be generalized.

Not only has histamine been isolated in increased concentration during experimental anaphylactic[13,25] shock and in clinical allergic conditions,[47,57,61] but it also has the following properties,[26] which the intermediary H-substance has been demonstrated to possess: It is stable to boiling with hydrochloric acid, is dialyzable, inactivated by incubation with histaminase or diamine oxidase, and inactivated by condensation with diazotized sulfanilic acid. It lowers the blood pressure of etherized atropinized cats, the contractile effect on the guinea pig intestine is inhibited by arginine (and other "antihistaminic" compounds), produces wheals in the human skin, and is found in highest concentration in the eosinophiles[14] (characteristic of allergic reactions).

Histamine alone cannot completely explain all of the manifestations of anaphylactic shock or clinical allergy.[15,26] The incoagulability of the blood in anaphylactic reactions, for example, is a phenomenon which requires the liberation of heparin[46] or a similar substance. Eczema and Contact Dermatitis cannot be as plausibly explained as urticaria and angioneurotic edema. Irreversible phenomena such as in periarteritis nodosa are not as well explained as the more common reversible type. In short, the histamine theory is a useful but not perfect working concept.

COUNTERACTION OF THE EFFECTS OF HISTAMINE

The rational practice of allergy attempts to interfere with the antigen-antibody union or control its location through proper elimination and desensitization procedures based upon etiological diagnosis so that the histamine problem does not arise. When such measures are not possible, not desired by the patient, or the results from them imperfect, the problem must be met. Counteraction of histamine is in many respects synonymous with the symptomatic control of allergic disorders and has been attacked on six fronts by the laboratory and clinician:

A. Decomposition of histamine with histaminase.
B. The use of antagonizing sympathetomimetic amines.
C. Partial neutralization with antispasmodics.
D. Increasing intolerance to histamine by physiological adaption.
E. Production of histamine-neutralizing antibodies by antigenic histamine complexes.
F. The administration of chemical blockers or "competitors," so-called "antihistaminic drugs."

A. The administration of the enzyme histaminase, obtained from the intestinal mucosa and kidneys of hogs, with the intent of decomposing histamine (presumably by deaminization) as soon as it is formed has had more laboratory[6] than clinical success. The difficulties encountered clinically are the necessity of fresh preparations and of continuous administration, since the enzyme is far more effective prophylactically than it is after clinical manifestations are under way. Clinical effectiveness of histaminase varies from fair in serum sickness[36] and urticaria to practically zero in asthma.

B. Sympathetomimetic amines of course counteract the parasympathetic stimulation of histamine (its cholinergic effect, if you will). Unfortunately their therapeutic indices are quite low. Epinephrine is the classical antagonist of this type both experimentally and clinically; its properties and uses are too well known to require recounting. Of the host of drugs belonging to this group, only Butanefrine (Ethyl-nor-epinephrine) parenterally[41] or by inhalation;[42] Ephedrine, Propadrine and Nethamine[40] orally; and Privine,[32] Ephedrine, Propadrine and

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Neosynephrine for intranasal use can be considered as useful additions to our therapeutic armamentarium. Each has some differences from epinephrine which can be used to clinical advantage. Butanefrine (Figure 1), for example, has the bronchodilator effect of epinephrine, with less of its central stimulation and none of its vasopressic effect. It is therefore useful in nervous people, small children, and in the presence of cardiovascular disease.[41] Privine has the advantage of prolonged vasoconstriction, but also has the disadvantage[33] of prolonged "rebound vasodilation." The aliphatic compound Tuamine (2-aminoheptane)[59] deserves mention as a useful substitute vasoconstrictor for people unable to tolerate the usual aromatic amines previously mentioned.[29]

PARTIAL NEUTRALIZATION WITH ANTISPASMODICS

C. Antispasmodics such as the xanthine group, papaverine, trasentin, etc., can be classified only as partial antagonists to histamine. Smooth muscle spasm induced by histamine is prevented or relaxed by such compounds experimentally and clinically, but the other pharmacologic effects of histamine are more or less unaffected. However, Theophylline Ethylenediamine, better known as Aminophylline, is most effective in asthma, and the same cannot be said generally for the newer "antihistaminic" drugs.

D. Attempts have been made to increase the physiological tolerance to histamine by its subcutaneous or intravenous administration. It was hoped that by these means the threshold to histamine stimulation could be raised above the point at which amounts ordinarily produced would be effective. Histamine, however, is a drug difficult to control, being highly diffusible and effective in such high dilution that unusual care must be exercised. Flushing, headache, urticaria and asthma may be induced while trying to prevent or alleviate same. Two general methods are in use: The subcutaneous method employs gradually ascending doses of the acid phosphate, starting in the 1:100,000 dilution and ending at 0.2 to 1.0 cc. of the 1:1,000. Dosage is then maintained at the level just short of producing symptoms. This has been notably successful in Horton's Histaminic Cephalalgia[45] and the primary-vasodilative type of migraine. Urticaria has shown some response, but this method has been distinctly disappointing in other allergic disorders. The intravenous method has been of aid only in migraine[11] and urticaria, and is usually used only in interims between attacks. 2.75 mg. of Histamine Acid Phosphate is diluted in 500 cc. of normal saline and given by intravenous drip over a four to eight hour period. Three or four treatments on alternate days are enough for semipermanent effect. Its proponents[11] claim tolerance is raised more effectively by the prolonged contact, but interruptions are often necessary during the actual treatment for the administration of ascorbic acid or small amounts of epinephrine intravenously, and antiacids orally for the gastric distress due to high acid secretion (peptic ulcer danger!?).

E. Histamine itself is not antigenic, but the production of neutralizing antibodies specific for histamine by the injection of an antigenic histamine protein complex has been accomplished. Landsteiner showed that the diazotization of simple chemicals and coupling to proteins resulted in the formation of antigenic complexes whose specificity was determined by the hapten portion.[49] Recently a method has been developed for the heightening and preserving of histamine antigenicity with simultaneous elimination of its usual toxic effects and the antigenicity of the associated protein. The first step was the despeciation of horse serum globulin by partial digestion with Taka-diastase at pH 3.8 followed by neutralization.[16] The resulting globulin produced no reaction in people known to be acutely allergic to horse serum and dander. Histamine was then combined with paranitrobenzoylchloride in chloroform and triethylamine. The resulting paranitrobenzoyl histamine was then reduced with ferrous sulfate and ammonia to yield para-aminobenzoyl histamine, which was then diazotized and coupled with the despeciated globulin. The resulting Histamine-azoprotein contains no free histamine, and is able to stimulate the formation of histamine neutralizing antibodies without producing histamine reactions.[35] Milton Cohen showed that these bodies were specific for the histamine, not the azo or protein portion of the complex, and that in certain patients histamine-azoprotein produced a capacity for very rapid histamine neutralization.[17] He also demonstrated an increased skin threshold to histamine administered by iontophoresis in histamine-azoprotein treated patients[17] and increased refractoriness to eserine stimulation.[18]

INDICATIONS FOR HISTAMINE-AZOPROTEIN THERAPY

Clinically histamine-azoprotein has shown its greatest value in the treatment of urticaria, angioneurotic edema and so-called physical allergy.[19,63] Unthinking enthusaists have harmed its cause by thoughtless use. Histamine-azoprotein is intended as an adjuvant to treatment rather than the sole remedy, and it is in no way a substitute for proper elimination and desensitization procedures based upon etiological diagnosis. When desensitization treatment produces suboptimal results because some antigen-antibody combination still takes place on cell surfaces with the release of histamine, histamine-azoprotein therapy is properly indicated. It is also indicated when the allergen cannot be identified after the most careful search, or in conditions in which the available antigens are weak, unstable or ineffective. In flea-bite sensitivity, to give an example of the last group, histamine-azoprotein has scored a notable success.[43] Apparently the amount of potential histamine neutralization engendered is enough to make the difference between comfort and misery.

F. The administration of chemical blockers or displacers is an old but fascinating subject in allergy, although to read the current newspapers and lay magazines one would infer that "antihistaminic" compounds were recent discoveries by completely altruistic drug companies.

Histamine antagonism is not necessarily synony-

mous with clinical relief, because histamine alone may not be the cause of the illness. Also, histamine has many physiological actions, and the compound under investigation may counteract only one or some but not others. Finally, the results of animal experimentation cannot be translated immediately into data for clinical use. In measuring antispasmodic action, for example, there are several pitfalls. Antispasmodics are of two general types:[60] The Musculotropic ones such as the nitrites and papaverine are tested against Histamine Phosphate ($2x10^{-6}$ gm./cc.) and Barium Chloride (10^{-4} gm./cc.). The Neurotropic ones such as atropine and scopolamine are tested against acetylcholine bromide (10^{-6} gm./cc.). The more peripherally acting musculotropic group would be of most interest to the allergist even without the concept of histamine antagonism. What may be relatively more musculotropic in one species may be relatively more neurotropic in another, and vica versa.

Experimentally the simple amino acids Histidine, Cysteine, and Arginine will all inhibit histamine-induced contractions of the guinea pig intestine,[27] but the amounts required for clinical use would be toxic. For example, 2,500 or more parts of arginine are required to counteract 1 part of histamine. Ascorbic acid (Vitamin C) has the same action but the amounts required are large experimentally and ineffective clinically[9] (except under special circumstances). Aminophylline and epinephrine, previously mentioned, also have this action, and from that standpoint could be considered as "antihistaminic" drugs.

The new "antihistaminic" drugs should more accurately be discussed under the heading of Dialkylaminoalcohol compounds because of their essential chemical structure. Antihistaminic phenolic ethers of amino alcohols have been known since 1910, but were too toxic for clinical use. Procaine (p-aminobenzoyl-diethylaminoethanol), which we are accustomed to regard only as a local anesthetic, is an antihistaminic drug particularly useful in serum sickness and urticaria.[1,65] Combinations of various aminoalcohols and chemical modifications of diphenylacetic acid have long been known to be antispasmodics. The aminoalcohol determines the nature of the action, while its intensity is modified by the acid group employed. If, for example, the diphenyl acetic acid ester of dimethylaminoethanol is prepared the result is a Neurotropic antispasmodic (Trasentin). If, on the other hand, the ester of 9,10-Dihydroanthracene-9-carboxylic acid is prepared the result is a Musculotropic one. Many of these compounds have more or less local anesthetic action, which appears to correlate more closely with musculotropic action than with other properties.[50]

The members of this recently publicized and growing family of "antihistaminics" of interest to us doing clinical allergy are Procaine, Benadryl, Pyribenzamine, Antergan, and Beta-dimethylaminoethyl 9,10-Dihydroanthracene-9-Carboxylate Hydrochloride, to be referred to hereafter as No. 887. Their structural formulae are shown in Figures 2 and 3.

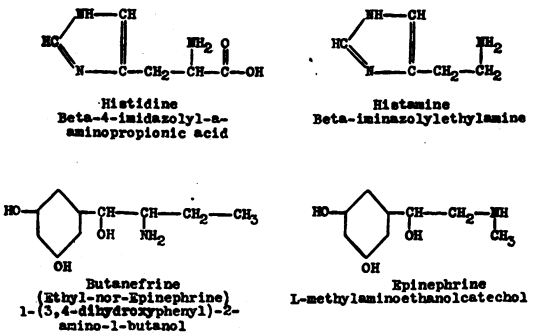

Figure 1.

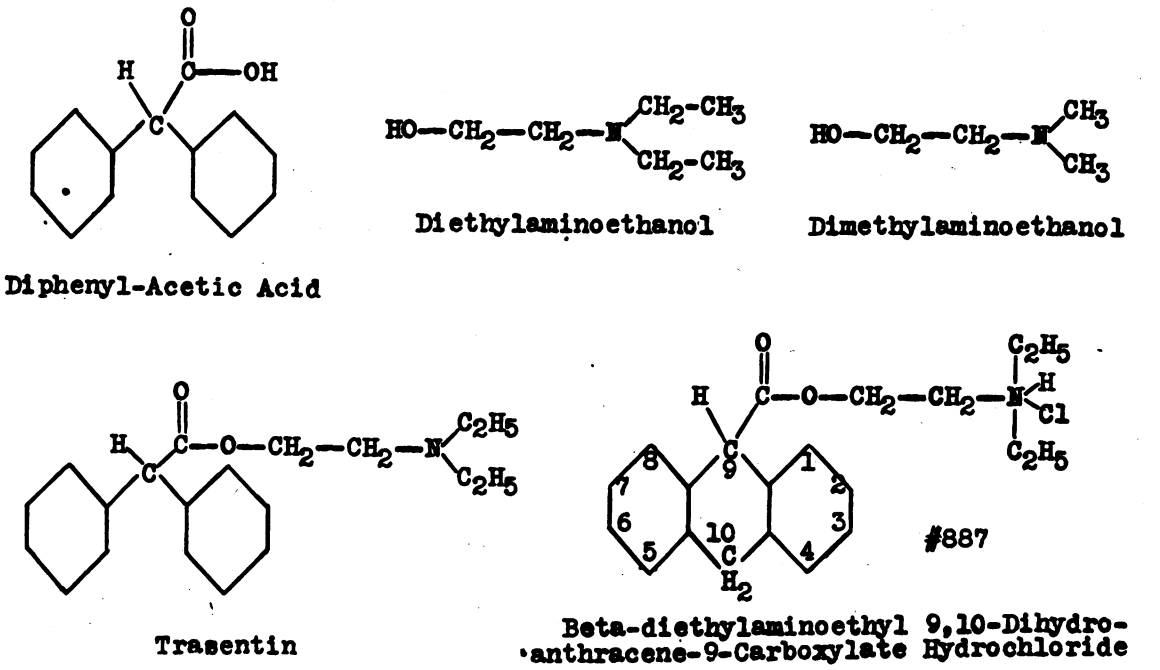

Figure 2.

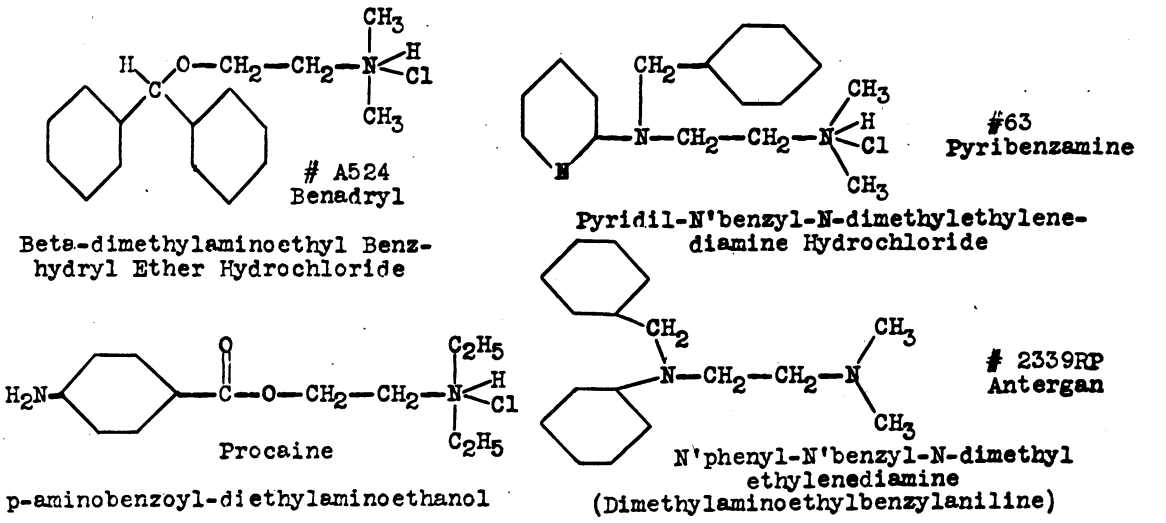

Figure 3.

Note the dimethylamine-ethane or diethylaminoethane group invariably present. All of them have local anesthetic action and secondary to that are cerebral depressants, a fact not sufficiently recognized. Their mode of action is a blocking one;[69] they combine with the site of action of histamine, occupying it primarily when given prophylactically or displacing it when given therapeutically. Histaminase is neither potentiated nor inactivated by their use and serum antibody levels are unaffected. Their absence of peripheral vasoconstrictor effect is evidence against a sympathomimetic effect. The release of histamine by antigen-antibody reaction is not prevented, and there is no evidence that the drugs combine with histamine itself.

Two standard methods adopted by laboratories in testing survival from ordinarily fatal histamine doses are: (a) the administration of a presumably protective dose of "antihistaminic" followed by histamine subcutaneously (or intravenously) and (b) a protective dose followed by histamine aerosol inhalation.[52] An examination of the comparative figures obtained by this last method would be of interest.

AEROSOLIZED HISTAMINE IN GUINEA PIGS

Dose in mg./kg. required to protect against asthma:

Epinephrine	0.2	
Ephedrine	>50	
Atropine	25	
Antergan (No. 2339RP)	1	
Benadryl (No. A524)	5	usually (10-15 reported)
Pyribenzamine (No. 63)	0.1	
No. 887	1	(approximately)
Procaine	Figures not available	

Needless to say, these figures are not directly transposable to the human. Other histamine induced phenomena have been studied with these drugs: inhibition of guinea pig intestine contractions; prevention of blood pressure drop in etherized atropinized cats; prevention of bronchoconstriction induced by lung perfusion; prevention of bronchoconstriction in barbitalized dogs intravenously induced; and prevention of vasodepressor effects of epinephrine. Decrease in gastric acidity

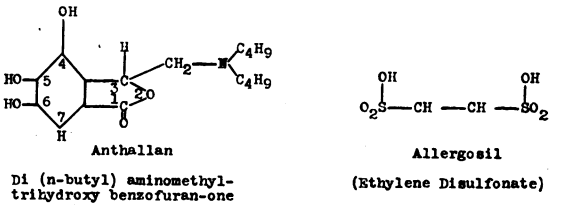

Figure 4.

and total secretion have been noted in animals and the human,[55] this effect being most marked with Benadryl. Except for Procaine, therapeutic indices are large and chronic toxicity studies thus far have been negative.

Procaine is the most familiar member, and, curiously enough, it is itself a fairly frequent cause of clinical allergy of the contact type. Its clinical use in allergy thus far has been limited to the treatment of serum sickness and urticaria.[1,65] One gram in 500 cc. normal saline is given intravenously over a two-hour period, and the treatment may be repeated daily. Of 16 cases of serum sickness, State[65] completely relieved ten and temporarily relieved four, and relieved six of seven cases of urticaria. In addition to "antihistaminic" action, one must consider the direct anesthetic action on the cells, decrease of acetylcholine liberated at terminals of efferent fibers, and epinephrine potentiating action.

For practical purposes, Benadryl and Pyribenzamine are clinically equivalent, 1 to 2 parts of either being required to counteract 1 part of histamine, depending on the circumstances. Because one has an ether linkage and the other a nitrogen linkage they are not exactly comparable pharmacologicaly. They are both effective orally, and clinical relief, when obtained, is evident in twenty to thirty minutes. Dosage varies from 50 to 500 mg. daily for an adult, the average effective plan being 50 mg. three or four times daily. The parenteral route is neither advisable nor ordinarily necessary, epinephrine being safer and more useful in emergencies, but Benadryl has been used in doses of 20 to 40 mg.

intravenously or intramuscularly. Benadryl is irritating in over 0.5 per cent concentration, so that its intranasal use is not advisable. Pyribenzamine has not been tried that way, but it seems inadvisable to use any local anesthetic intranasally for symptomatic relief.

It is difficult to give the percentages of various conditions in which relief may be expected from Benadryl or Pyribenzamine, because the reporting investigators varied in their dosages, in their definitions of the conditions treated, and in their criteria of relief. Here are reasonable "round-figure" averages compiled from over 2,600 cases* in current medical literature. How much allowance has been made for the variability of allergic manifestations and spontaneous improvement is unknown.

Urticaria and angio-neurotic edema, acute	85%
Urticaria and angio-neurotic edema, chronic	75%
Dermographism	80%
Atopic eczema (the pruritus only)	50%
Contact dermatitis (the pruritus only)	60%
Seasonal allergic rhinitis (hay fever)	60%
Perennial allergic rhinitis (extrinsic cause demonstrated)	40%
Vasomotor rhinitis-hyperesthetic rhinitis (intrinsic?)	40%
Seasonal asthma (associated with hay fever)	45%
Perennial asthma (extrinsic etiology demonstrated)	30%
Perennial asthma of unknown etiology (intrinsic?)	30%
Asthma precipitated by acute (upper) respiratory infection	Zero %

The number of cases of migraine, histaminic cephalalgia, gastro-intestinal allergy, serum sickness, and pruritus of miscellaneous origin thus far treated do not permit of reliable conclusions; the statistically-minded may use 50 per cent, 60 per cent, 85 per cent (Benadryl)-28 per cent (Pyribenzamine), eighty per cent and sixty per cent, respectively, temporarily. Of the two drugs, only Benadryl has been used clinically to depress gastric secretory activity in gastro-intestinal conditions.[55]

Maximum effectiveness is shown in the conditions exhibiting wheal formation, as might be expected. The perennial rhinitis and asthma cases include both those in which a definite allergic cause can be demonstrated and those of unknown origin. A clinical impression is that results in the latter group are much poorer than in the former. Asthma precipitated by acute respiratory infection is conspicuously unrelieved, and the result in asthma other than that associated with pollinosis are not spectacular. All of these figures include both total and partial relief; about one-third of those relieved are only partially so. All relief is purely temporary, the symptoms usually recurring promptly in the chronic cases on discontinuance of treatment.

We know of Antergen only from the reports of French investigators.[5,12,24,38] The general properties are the same as those of Pyribenzamine, but four or five times larger doses are required clinically. The more recent Neoantergan is claimed to be more effective and less toxic than Antergan.[7,23]

The side effects of these drugs are by no means minor, as they limit their clinical usefulness and necessitate certain precautions in directions and occasionally counteracting adjuvants (which are in themselves not innocuous). The most frequently occurring side-effects are sleepiness of varying degree, nausea and vomiting, dizziness, headache, dry mouth, nervousness and gastro-intestinal cramps. Various authors have reported incidences of 20 per cent to 70 per cent of their series having side-effects. The majority, including the author, note about 50 per cent. Of these, one-tenth to one-half have to discontinue the drug, again the figures depending on the author's estimate of what is serious or dangerous. The order of reactions with Pyribenzamine is: Sleepiness, nausea, headache, gastro-intestinal cramps, dizziness, nervousness and dry mouth. The order with Benadryl is: sleepiness, dry mouth, nervousness, dizziness and weakness.

Whereas the hypnotic effect is a useful one at night, it is dangerous during the day and can be the cause of accidents.[64] The first few doses should always be taken while a person is in a safe place under observation (not necessarily by a physician), and not while at work around such things as ladders, scaffoldings, machinery, etc. Counteracting these effects with caffeine or amphetamine stimulation may merely add the undesirable effects of these drugs, such as nervousness and loss of appetite. Sedatives must, of course, be used cautiously, and one must be doubly careful about the administration of anesthetics for emergency operations.

The indications for the use of Benadryl and Pyribenzamine may be summed up as follows:

(a) The control of diffuse skin irritability and Dermographism so that the performance of specific skin tests is possible.
(b) The control and prevention of testing and treatment reactions.
(c) The maintenance of allergy patients in comfort for a few weeks until specific desensitization becomes effective.
(d) The control of acute transient allergic manifestations.
(e) The control of pruritus in general in order to minimize scratching and the attendant danger of infection.
(f) The control of urticaria following sulfonamides, antibiotics,[62] organ extracts, serums and indispensable drugs.
(g) Infrequently, the control of gastric acidity.

The possibility of acquired allergy to the drugs themselves is not fantastic, as urticaria from both has been noted. Anemia resulting from the anacidity is possible from long continued use, though how probable that is we do not yet know. The aromatic rings and coal tar origin suggest the possibility of agranulocytosis, and of caution in administration to salicylate-sensitive persons.

Beta-Diethylaminoethyl 9,10-Dihydroanthracene-9-Carboxylate Hydrochloride (No. 887) cannot yet receive a general comparison with Pyribenzamine and Benadryl, because it has been clinically evaluated only in asthma.[44] Since the supply available was limited, it was tried only in this condition, in which Pyribenzamine and Benadryl were relatively ineffective. Experimentally it is about 20 times more potent than papaverine and about one-fifth as effective as epinephrine in relaxing spasm of the bronchioles induced by histamine.[10] From the viewpoint of acute toxicity there is a wide margin

* 2, 3, 20, 22, 31, 34, 37, 48, 51, 53, 54, 56, 58, 66, 67, 68.

of safety, but the hypnotic action (also a local anesthetic!) is a limiting factor for daytime use. No adverse effects or habituation have been observed from prolonged administration. Oral administration to 90 cases of asthma of varying grades of severity provided 80 per cent of them with definite benefit, a marked contrast to Benadryl and Pyribenzamine. The optimum dose on retiring appears to be 200 mg., but during the day 100 mg. every four hours appears to be enough unless the asthma is quite severe.

By way of conclusion, some philosophy may be added to allergy. Up to 1932, 165 methods of inhibition of anaphylaxis had been described. In the last fifteen years there have probably been hundreds more. Out of all of these relatively few have proven their value. The successes have been characterized by prolonged preliminary investigation in ethical laboratories and clinical trial by objectively-minded, conservative allergists. The possibilities inherent in the compounds could be predicted fairly well from their chemical structure and groupings. Conversely, unwarranted claims can often be shown up by a consideration of chemical structure, concentrations employed and methods of use.

The desire of newspapers to present information that is startling rather than factual has led to the recent unwarranted publicity for Anthallan, purportedly an "antihistaminic" drug, and Ethylene Disulphonate (Allergosil), not "antihistaminic" but unfortunately confused with them (Figure 4). Supposedly present in allergic individuals is a "defect in intracellular oxidation-reduction mechanisms and disordered carbohydrate breakdown." Ethylene disulphonate is the synthetic catalyst proposed to correct this regrettable defect.[30] Small amounts in a dilution $1x10^{15}$ in distilled water are administered intramuscularly. The temporary pain and muscular fibrillation observed are no doubt due to the practically pure water injected (and at what a price!) A few enthusiasts have published papers of questionable scientific worth, but the consensus of opinion[4,8,21] of recognized allergists is that the compound has no value and cannot be distinguished in its effects from distilled water.

Anthallan (Di (n-butyl) aminomethyl-trihydroxy benzofuranone) is purported to have antihistaminic effect pharmacologically, but it is as clinically inactive as its structural formula is unpromising. Questionable criteria of allergy were used in the conduct of the clinical investigations.[28] In fact one investigator claims that "not only can hyperesthetic rhinitis [please define that term for us!] be treated simply and effectively with this drug, but the diagnostic problem can be ignored."[39] With these noble words allergists are wafted from usefulness into obsolescence.

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REFERENCES

1. Appelbaum, E., Abraham, A., and Sinton, W.: A Case of Serum Sickness Treated with Procaine Intravenously, J.A.M.A., 131:1274 (Aug. 17), 1946.

2. Arbesman, C. E., Koepf, G. F., and Lenzner, A. R.: Clinical Studies with Pyribenzamine, J. Allergy, 17:275 (Sept.), 1946.

3. Arbesman, C. E., Koepf, G. F., and Miller, G. E.: Some Antianaphylactic and Antihistaminic Properties of N'Pyridil, N'Benzyl, Dimethylethylenediamine Monohydrochloride (Pyribenzamine), J. Allergy, 17:203 (July), 1946.

4. Archibald, H. C.: Ethylene Disulphonate and Sterile Distilled Water Controls in the Treatment of Children's Allergies, Arch. Pediat, 62:219, 1945.

5. Aubertin, E.: Une Nouvelle Médication dans le Traitement des Maladies par Hypersensibilité: Les Antihistaminiques de Synthése, J. de Méd. de Bourdeaux, 119:606, 1942.

6. Best, C. H. and McHenry, E. W.: The Inactivation of Histamine, J. Physiol., 70:349 (Dec. 4), 1930.

7. Bovet, D., Horclois, R., and Watthert, F.: Proprietes Antihistaminique de la N-p-methoxybenzyl-N-dimethylaminoethyl a Amino-pyridine, Compt. Rend. Soc. de Biol., 138:99, 1944.

8. Brenner, H. H. and Stoesser, A. V.: Ethylene Disulphonate in Chronic Asthma, Ann. Allergy, 4:179 (May-June), 1946.

9. Brown, E. A.: The Vitamins and Allergy, Ann. Allergy, 2:156 (March-April), 1944.

10. Burtner, R. R. and Cusic, J. W.: Antispasmodics. II—Basic Esters of Some Polynuclear Carboxylic Acids, J. Am. Chem. Soc., 65:1582, 1943.

11. Butler, S. and Thomas, W. A.: Intravenous Histamine in the Tretment of Migraine. Preliminary Observations, J.A.M.A., 128:173 (May 19), 1945.

12. Celice, J., Perrault, M., and Durel, P.: Utilisation Clinique des Antihistaminiques de Synthése, Bull. et Mém. Soc. Méd. d. Hôp. de Paris, 58:284, 1942.

13. Code, C. F.: The Histamine Content of the Blood of Guinea Pigs and Dogs During Anaphylactic Shock, Am. J. Physiol., 127:78 (Aug.), 1939.

14. Code, C. F. and MacDonald, A. D.: The Histamine-Like Activity of Blood, Lancet., 2:730, 1937.

15. Code, C. F.: The Mechanism of Anaphylactic and Allergic Reactions, Ann. Allergy, 2:457 (Nov.-Dec.), 1944.

16. Coghill, R. D., Fell, N., Creighton, M., and Brown, G.: The Elimination of Horse Serum Specificity from Antitoxins, J. Immunol., 39:207, 1940.

17. Cohen, M. B. and Friedman, H. J.: Antibodies to Histamine Induced in Human Beings by Histamine Conjugates, J. Allergy, 14:195, 1943.

18. Cohen, M. B. and Friedman, H. J.: Immunity Against H-Substance, J. Allergy, 15:245, 1944.

19. Cohen, M. B.: Urticaria and Angioneurotic Edema. A Summary of Our Present Knowledge, Ohio State M. J., 39:1120, 1943.

20. Committee on Pharmaceuticals and Medicaments of the American Academy of Allergy: A Report of the Clinical Studies on the Use of Pyribenzamine in Allergic Diseases, J. Allergy, 17:325 (Sept.), 1946.

21. Council Report: Ethylene Disulphonate, J.A.M.A., 131:1495 (Aug. 31), 1946. Editorial: Ethylene Disulphonate and Allergy, J.A.M.A., 131:1502 (Aug. 31), 1946.

22. Curtis, A. C. and Owens, B. B.: Benadryl in Treatment of Urticaria, Arch. Dermat. & Syph., 52:239, 1945.

23. Decourt, M. J.: La Medication Antihistaminique, La Semaine des Hospit. de Paris, 21:707, 1945.

24. Decourt, P.: Action de Bases Antagonistes de l'Histamine Sur Quelques Maladies Liées à des Réactions d'Hypersensibilité, Bull. et. Mém. Soc. Méd. d. Hôp. de Paris, 58:265, 1942.

25. Dragstedt, C. A. and Gebauer-Fuelnegg, E.: Studies in Anaphylaxis. I.—The Appearance of a Physiologically Active Substance During Anaphylactic Shock, Am. J. Physiol, 102:512, 1932.

26. Dragstedt, C. A.: The Significance of Histamine in Anaphylaxis, J. Allergy, 16:69 (March), 1945.

27. Edlbacher, S., Jucker, P., and Baur, H.: Die Beinflussung der Darmreaktion des Histamins Durch Aminosauren, Hoppe Seylers Ztschr. f. Physiol. Chem., 247:63, 1937.

28. Editorial: Anthallan and Rhinitis, J.A.M.A., 131: 745 (June 29), 1946.

29. Engelsher, D. L.: Unusual Ephedrine Reaction, New York State J. Med., 45:307, 1945.

30. Evans, G., Bodman, J., and Maisin, J. H.: The Chemical Control of Allergy, Med. Press and Circular CCIII, May 29 and June 5, 1940.

31. Eyermann, C. H.: Clinical Experiences with a New Antihistaminic Drug (Benadryl), J. Allergy, 17:210 (July), 1946.

32. Fabricant, N. D. and Van Alyea, O. E.: A Note on the Evaluation of Privine Hydrochloride As a Nasal Vasoconstrictor, Am. J. Med. Sci., 205:122 (Jan.), 1943.

33. Feinberg, S. M. and Friedlaender, S.: Nasal Congestion from Frequent Use of Privine Hydrochloride, J.A.M.A., 128:1095 (Aug. 11), 1945.

34. Feinberg, S. M. and Friedlaender, S.: Relief of Dermographism and Other Urticarias of Histamine Origin by a Synthetic Benzhydryl Alkamine Ether, J. Allergy, 16:296 (Nov.), 1945.

35. Fell, N., Rodney, G., and Marshall, D. E.: Histamine-Protein Complexes; Synthesis and Immunologic Investigation. I.—Histamine-Azoprotein, J. Immunol., 47:237, 1943.

36. Foshay, L. and Hagebusch, O. E.: Histaminase in the Treatment of Serum Sickness, J.A.M.A., 112:2398 (June 10), 1939.

37. Friedlaender, S. and Feinberg, S. M.: Histamine Antagonists. III.—The Effect of Oral and Local Use of Benadryl on the Whealing Due to Histamine, Antigen-Antibody Reactions, and Other Whealing Mechanisms. Therapeutic Results in Allergic Manifestations, J. Allergy, 17:129 (May), 1946.

38. Gaté, J., Thiers, H., Cuilleret, P., and Pellerat, J.: Recherches Sur l'Action de Nouveaux Composés Antihistaminiques de Synthése, J. de Méd., de Lyon, 23:401, 1942.

39. Ghiselin, A. D., Jr.: The Treatment of Seasonal and Non-Seasonal Hyperesthetic Rhinitis with Anthallan, Bull. New York Acad. Med., 22:320 (June), 1946.

40. Hansel, F. K.: Nethamine Hydrochloride and Theophylline Isobutanolamine in the Treatment of Nasal Allergy and Asthma, Ann. Allergy, 1:199 (Nov.-Dec.), 1943.

41. Hartman, M. M.: Parenteral Use of Butanefrine in Asthma. A Comparison with Epinephrine, Ann. Allergy, 3:366 (Sept.-Oct.), 1945.

42. Hartman, M. M.: Ethyl-nor-Epinephrine by Inhalation for Bronchial Asthma; A Comparison with Epinephrine, J. Allergy, 17:106 (March), 1946.

43. Hartman, M. M.: Fleabite Reactions—Clinical and Experimental Observations and Effect of Histamine-Azoprotein Therapy, Ann. Allergy, 4:131 (March-April), 1946.

44. Hartman, M. M.: Anti-Asthmatic Effects of Beta-Diethylaminoethyl 9, 10-Dihydroanthracene-9-Carboxylate Hydrochloride. A New Synthetic Antispasmodic, Ann. Allergy. To be published.

45. Horton, B. T.: The Use of Histamine in the Treatment of the Specific Types of Headaches, J.A.M.A., 116: 377 (Feb. 1), 1941.

46. Jacques, L. B. and Waters, E. T.: The Isolation of Crystalline Heparin from the Blood of Dogs in Anaphylactic Shock, Am. J. Physiol., 129:389, 1940.

47. Katz, G. and Cohen, S.: Experimental Evidence for Histamine Release in Allergy, J.A.M.A., 117:1782 (Nov. 22), 1941.

48. Koelsche, G. A., Prickman, L. E., and Carryer, H. M.: The Symptomatic Treatment of Bronchial Asthma and Hay Fever with Benadryl, Proc. Staff Meet., Mayo Clin., 20:432 1945.

49. Landsteiner, K. and Lampl, H.: Über die Abhängigkeit der Serologischen Spezifizität von der Chemischen Struktur. XII.—Mitteilung Über Antigene, Biochem. Ztschr., 86:343, 1918.

50. Lehmann, G. and Knoefel, P. K.: The Spasmolytic and Local Anesthetic Action of Some Derivatives of Fluorene-Carboxylic Acid and Related Compounds, J. Pharmac. & Exper. Therap., 74:274 (March), 1942.

51. Levin, S. J.: Benadryl. Its Use in Allergic Diseases, J. Allergy, 17:145 (May), 1946.

52. Loew, E. R., Kaiser, M. E., and Moore, V.: Synthetic Benzhydryl Alkamine Ethers Effective in Preventing Fatal Experimental Asthma in Guinea Pigs Exposed to Atomized Histamine, J. Pharmacol. & Exper. Therap., 83:120, 1945.

53. Logan, G. B.: The Use of Benadryl in Treating Some of the Allergic Diseases of Childhood, Proc. Staff Meet., Mayo Clin., 20:436, 1945.

54. McElin, T. W. and Horton, B. T.: Clinical Observations on the Use of Benadryl, Proc. Sta- Meet., Mayo Clin., 20:417, 1945.

55. McGavack, T. H., Elias, H., and Boyd, L. J.: The Influence of Benadryl on Gastric Acidity, Gastroenterology, 6:439, 1946.

56. O'Leary, P. A. and Farber, E. M.: Benadryl in the Treatment of Urticaria, Proc. Staff Meet., Mayo Clin., 20:429, 1945.

57. Parrott, J. L.: Les Manifestations de l'Anaphylaxie et les Substances Histaminiques, Paris, 1938, Bailliére Edit.

58. Pinkus, H.: Benadryl in the Treatment of Erythema Exudativum Multiforme, Ann. Allergy, 4:288 (July-Aug.), 1946.

59. Proetz, A. W.: Amino-Heptane As a Nasal Vasoconstrictor, Ann. Otol., Rhin. & Laryng., 51:112, 1942.

60. Raymond, A. L.: Recent Developments in Synthetic Antispasmodics, J. Am. Pharmaceut. Assoc., Scientific Ed., 32:249 (Oct.), 1943.

61. Rose, B.: Studies on Blood Histamine in Patients with Allergy. II.—Alterations in the Blood Histamine in Patients with Allergic Disease, J. Clin. Invest., 20:419, 1941.

62. Scheinberg, D.: Generalized Angioneurotic Edema Due to Penicillin Inhalations Treated with Benadryl, J.A.M.A., 132:78 (Sept. 14), 1946.

63. Sheldon, J. M., Fell, N., Johnston, J. H., and Howes, H. A.: A Clinical Study of Histamine-Azoprotein in Allergic Disease, J. Allergy, 13:18, 1941.

64. Slater, B. J. and Francis, N.: Benadryl, A Contributing Cause of an Accident, J.A.M.A., 132:212 (Sept. 28), 1946.

65. State, D. and Wangensteen, O. W.: Procaine Intravenously in Treatment of Delayed Serum Sickness, J.A.M.A., 130:990 (April 13), 1946.

66. Thacker, E. A.: Evaluation of Benadryl as a Therapeutic Agent for Vasomotor and Allergic Rhinitis, Arch. Otorhinolaryng., 43:597 (June), 1946.

67. Todd, L. C.: Some Clinical Observations on the Use of Benadryl for the Symptomatic Relief of Allergic Conditions, Ann. Allergy, 4:282 (July-Aug.), 1946.

68. Waldbott, G. L.: Clinical Results with Benadryl, J. Allergy, 17:142 (May), 1946.

69. Wells, J. A., Morris, H. C., Bull, H. B., and Dragstedt, C. A.: Observations on the Nature of the Antagonism of Histamine by B-dimethylaminoethyl Benzhydryl Ether (Benadryl), J. Pharmacol. & Exper. Therap., 85:122, 1945.